UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Note to Reader
January 15, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply. EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack E. Housenger, Acting Director
Special Review and Reregistration Division

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HED DOC NO. 012627

DATE: May 27, 1998

MEMORANDUM

SUBJECT: **PROPETAMPHOS**: Report of the Hazard Identification Assessment Review Committee

FROM: Linda L. Taylor, Ph.D.
Reregistration Branch I
Health Effects Division (7509C)
and
Jess Rowland, Executive Secretary
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THRU: K. Clark Swentzel, Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Michael Metzger, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Robert Travaglinia
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

PC Code: 113601

On April 29, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee [HIARC] evaluated the toxicology data base of Propetamphos, re-assessed the Reference Dose [RfD] established in 1986, and selected the toxicological endpoints for acute dietary and occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to Propetamphos as required by the Food Quality Protection Act [FQPA] of 1996. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were: Karl Baetcke, William Burnman, Robert Fricks, Karen Hamernik, Susan Makris, Nancy McCarroll, Mike Mtezger, Jess Rowland [Executive Secretary], and Clark Swentzel [Chairman]. Member *in absentia* Melba Morrow, John Redden. Data were presented by Linda Taylor of Reregistration Branch I.

Also in attendance were Steve Weiss and Robert Travaglinia.

Data Presentation and Report Presentation: ___________________________

Linda L. Taylor, Ph.D.
Toxicologist

Report Concurrence: ___________________________

Jess Rowland
Executive Secretary

I. INTRODUCTION

On April 29, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee [HIARC] re-assessed the existing RfD and established the toxicology endpoints for acute dietary and occupational and residential exposure risk assessments pursuant to the Food Quality Protection Act [FQPA] of 1996. The HIARC also addressed the potential enhanced sensitivity of infants and children, as required by FQPA.

The HED RfD Peer Review Committee [1986] previously established the RfD of 0.005 mg/kg/day, based on the same mouse study and the 6-month dog study [NOEL of 0.05 mg/kg/day and an uncertainty factor of 10 to account for the cholinesterase depression differences in the extrapolation from mouse to man].

II. HAZARD IDENTIFICATION

A. Acute Reference Dose [RfD]

Study Selected: 4-week oral study in the mouse §none

MRID No.: 00117996

Executive Summary: In the 8-week preliminary toxicity [dose range-finding] study in mice [MRID 00117996], Propetamphos [91.4% a.i.] was administered to 4 Charles River CD-1 mice/sex/group at actual dose levels of 0, 1, 7, 15, 28, and 59 [fed this level during weeks 1-5; increased to 103 mg/kg/day during weeks 6-7 and increased to 172 mg/kg/day during week 8] mg/kg/day. The study was terminated on day 58 of the study. In a subsequent 4-week study performed to determine the NOEL for cholinesterase inhibition, 5 CD-1 mice/sex/dose were administered Propetamphos [91.8% a.i.] at dose levels of 0. 0.05 [actual intake was 0.027 mg/kg/day], 0.1, and 0.5 mg/kg/day for 26 days.

8-Week Study: No explicit signs of cholinesterase inhibition were exhibited at any dose level in either sex. During the 8th week when the high-dose level was increased to 172 mg/kg/day, one female [day 52; no clinical signs] and one male [day 56; on day 55 weakness, decreased locomotor activity] died. Another high-dose female displayed decreased locomotor activity and weakness on day 56 but survived until study termination. Decreased body weight [♂♂ 64%/♀♀ 67% of control overall] and body-weight gain [♂♂ <5%/♀♀ 6% of control overall] were observed at the highest dose level [59-172 mg/kg/day] in both sexes throughout the study. Decreased body weights [87%-90%] were also observed in females at the 28 mg/kg/day dose level during weeks 3 to 5. At the highest dose level [both sexes] decreased food intake was observed during weeks 6 to 8. In addition to decreased body weight/gain, the only other dose-related effects observed in the 8-week study were (1) a dose-related decrease in plasma cholinesterase activity in both sexes [♂♂ 34%-92%/♀♀ 29%-95%] at both time intervals [weeks 4 and 7; significant at all dose levels]; (2) a dose-related decrease in erythrocyte cholinesterase activity in both sexes [♂♂ 62%-92%/♀♀ 46%-95%] at dose levels of 7 mg/kg/day and above at both time intervals and in females at the 1 mg/kg/day dose level [LDT] at 7 weeks; (3) a dose-related decrease in cholinesterase activity in brain in both sexes [♂♂ 29%-82%/♀♀ 39%-89%] at dose levels of 7 mg/kg/day and above; and (4) a dose-related decrease in liver cholinesterase activity in both sexes [♂♂ 30%-81%/♀♀ 14%-86%] at dose levels of 7 mg/kg/day and above and in males at the 1 mg/kg/day dose level [LDT].

4-Week Study: No treatment-related effects were observed on body weight or body-weight gain in either sex, and food consumption was not adversely affected in either sex. No cholinesterase inhibition was observed in the liver in either sex, and only females at the high-dose level displayed a slight decrease in cholinesterase activity in the plasma and erythrocytes.

No ophthalmoscopic, hematology, clinical chemistry, urinalysis parameters were monitored, organ weights were not measured, and no histopathology was performed in either study. When the findings in the 4-week subsequent study are combined with those of the 8-week study, **the NOEL for liver, erythrocyte, and plasma cholinesterase inhibition is 0.5 mg/kg/day and the LOEL for liver, erythrocyte, and plasma cholinestrerase inhibition is 1 mg/kg/day.** For brain cholinesterase inhibition, although no inhibition was noted in the 8-week study at 1 mg/kg/day, there was a dose-related inhibition in the 4-week study. **The NOEL for brain cholinesterase inhibition is 0.05 mg/kg/day, and the LOEL for brain cholinesterase inhibition is 0.1 mg/kg/day.**

Dose and Endpoint for Risk Assessment: NOEL = 0.05 mg/kg/day, based on inhibition of brain cholinesterase activity at four weeks (earliest time of measurement; 15% for males; 28% for females) at the next highest dose (0.1 mg/kg/day; LOEL)

Comments about Study/Endpoint: In the acute neurotoxicity study in rats, no cholinesterase activity measurements were performed; therefore, the 4-week mouse study provides the earliest time point for this endpoint.

Uncertainty Factor (UF): 100

$$\textbf{Acute RfD} = \frac{0.05\ \text{mg/kg}}{100} = \mathbf{0.0005\ mg/kg}$$

This risk assessment is required.

B. Chronic RfD

Study Selected: chronic toxicity/carcinogenicity §83-5

MRID No.: 00063021 and 00102928

Executive Summary: In the carcinogenicity/toxicity study in mice [MRID 00102928], Propetamphos [91.8% a.i.] was administered to 50 weanling Charles River CD-1 mice/sex/group at dose levels of 0, 0.05 [only 10/sex to evaluate NOEL for cholinesterase activity], 1.0, 6.0, and 21.0 mg/kg/day.

Additional groups of 10 mice/sex/group were placed on test for the 12- and 18-month interim sacrifices [not the 0.05 mg/kg/day group], and an additional 10 mice/sex/group [except the 0.05 and 6.0 mg/kg/day groups] were placed on test to assess cholinesterase activity in plasma, erythrocyte, liver, and brain. The study was terminated at ≈91 weeks.

No clinical signs of toxicity were observed among the groups in either sex, although the high-dose mice of both sexes displayed less inactivity than the controls and other dose groups. There was no adverse effect on the survival of the males, but the high-dose females [60%] displayed a greater mortality rate than the control females [45%] and a shorter [median] survival time [623 days vs 645, respectively]. There were no adverse effects on body weight or body-weight gain in either sex. Food consumption was decreased and considered treatment-related throughout the study at the 21 mg/kg/day dose level in both sexes and at the 6 mg/kg/day dose level in males, which may be attributed to a palatability problem and/or increased spillage [although the reason for this was not pursued], and from week 25 on, at the 1 mg/kg/day dose level also (both sexes)]. There were no consistent differences noted in the hematology and clinical chemistry parameters measured in either sex, nor were there any consistent findings in organ weights. Males at the high-dose level displayed a significant increase in brain weight compared to the control at week 52 only; brain weight was comparable among the female groups at the 52-, 78-, and 93-week sacrifices and among the male groups at the 78- and 93-week sacrifices. High-dose females displayed a significant decrease [86% of control] in heart weight at the 52-week sacrifice and a non-significant decrease at 78- and 93-week sacrifices [93% and 95% of control, respectively]. The only dose-related effect observed in both sexes [at dose levels of 1 mg/kg/day and above] was the inhibition of erythrocyte [♂♂ 20%-87%/♀♀ 33%-91%], plasma [♂♂ 23%-89%/♀♀ 20%-87%], brain [♂♂ 51%-74%/♀♀ 58%-79%], and liver [♂♂ 44%-69%/♀♀ 25%-50%] cholinesterase activities in both sexes throughout the study. There was an increase in the incidence of brain vacuolization in the high-dose males, myeloid hyperplasia [bone marrow] in the mid-dose males and in the high-dose of both sexes, neural vacuolization in the high-dose females, and mucosal hyperplasia [duodenum] in the mid- and high-dose females. There was no apparent increase in the incidence of tumors in either sex at dose levels that caused significant cholinesterase inhibition. **The systemic NOEL for effects other than cholinesterase inhibition is 1 mg/kg/day, and the systemic LOEL is 6 mg/kg/day, based on an increased incidence of myeloid hyperplasia in males and mucosal hyperplasia in the duodenum in females. At the 21 mg/kg/day dose level, females displayed an increased incidence of myeloid hyperplasia and neural vacuolation, and the 21 mg/kg/day dose level males displayed a slight increase in the incidence of brain vacuolation. The NOEL for cholinesterase inhibition is 0.05 mg/kg/day, and the LOEL is 1 mg/kg/day, based on erythrocyte, plasma, and brain cholinesterase inhibition.**

Dose and Endpoint for Establishing RfD: NOEL = 0.05 mg/kg/day, based on inhibition of cholinesterase activities in plasma, red blood cells, and brain at the next highest dose (1.0 mg/kg/day; LOEL)

Uncertainty Factor(s): 100 [10 for intraspecies variation and 10 for interspecies variation]

Chronic RfD: $\frac{0.05 \text{ mg/kg/day}}{}$ = **0.0005 mg/kg/day**

Comments about Study/Endpoint/Uncertainty Factor: The endpoint is a consistent finding and the NOEL is the same as observed in the 4/8-week study and represents the lowest NOEL for this parameter. The NOEL for cholinesterase inhibition in the rat is 0.3-0.6 mg/kg/day [2-generation reproduction study, rat 90-day neurotoxicity study, rat chronic toxicity study] and in the dog is 0.08-0.69 mg/kg/day [6-month and one-year].

This risk assessment is required.

C. Occupational/Residential Exposure

1. Dermal Absorption

No dermal absorption study is available. The Committee concluded that a dermal absorption rate of 100% was appropriate, based on the lack of a dermal absorption study, the fact that the mouse and dog appear to be the sensitive species, cholinesterase inhibition was not determined in the acute neurotoxicity study in rats, and there are no comparable cholinesterase measurements in the rabbit studies [21-day dermal and developmental toxicity] to assess dermal absorption.

Dermal Absorption Factor: 100%

2. Short-Term Dermal - (1-7 days)

Study Selected: 6-month dog [at 4 weeks] §83-1/none

MRID No.: 00039595

Executive Summary: In a six-month toxicity study, four beagle dogs/sex/group were supposed to be administered propetamphos technical (91.8% a.i.) in the diet at doses of 0, 6, 12 or 24 ppm for six months. However, after six weeks, the 6 and 12 ppm doses were reduced to 2 and 4 ppm, respectively, because blood cholinesterase levels had decreased below tolerance limits (±20%) in these groups. The average actual daily intake for males was 89, 176 and 692 μg/kg/day; for females, the dosages were 83, 165 and 702 μg/kg/day, respectively, which corresponded to dosages of 3.4, 6.8 and 28 ppm in the diet.

There were no treatment-related changes in clinical signs, body weight, food or water consumption, clinical laboratory parameters (except cholinesterase) and post-mortem findings. Plasma and RBC cholinesterase (ChE) were measured pre-treatment and at Weeks 4, 6, 8, 12, 20 and 26 of treatment. At Week 4, plasma ChE was significantly ($p \leq 0.01$ or 0.05) decreased in both sexes of all treated groups, but not in a dose-related manner (males: 25-52%; females: 28-34%). At Week 4, RBC ChE was significantly decreased in both sexes of the mid- and high-dose groups (males: 43-46%; females: 31-53%). At Week 6, plasma ChE was significantly decreased in the high-dose group males (31%)

and all treated females (34-37%). Also at Week 6, RBC ChE was significantly decreased in both sexes of the mid- and high-dose groups (males: 38-39%; females: 31-51%). After the reduction in dosage at Week 6 for the mid- and high-dose groups, plasma ChE was significantly decreased in both sexes of the high-dose group (males: 36-39%; females: 39%) during Weeks 12 and 26, but not at Weeks 8 and 20. RBC ChE was significantly decreased in both sexes of the high-dose group (males: 50-51%, Weeks 8, 12 and 26; females: 56-60%, Weeks 8, 12 and 26) and occasionally in both sexes of the mid-dose group (males: 36-43%; females: 23-31%). Homogenates of the cerebellum and cerebrum were analyzed for ChE levels. There was no evidence of a treatment-related effect in the cerebellum. ChE levels in the cerebrum was significantly decreased in the mid- and high-dose group males (36 and 42%, respectively). Although not statistically significant, the decrease in cerebrum ChE for the 24 ppm group females (65%) was judged to be biologically significant. Analysis of liver homogenates for both acetylcholinesterase and butyryl cholinesterase showed significantly decreased levels of both in the high-dose group males and females and the mid-dose group females.

The NOEL for plasma cholinesterase inhibition was 4 ppm (males: 0.176 mg/kg/day; females: 0.165 mg/kg/day. The LOEL was 24 ppm (males: 0.692 mg/kg/day; females: 0.702 mg/kg/day). The NOEL for RBC cholinesterase inhibition was 2 ppm (males: 0.089 mg/kg/day; females: 0.083 mg/kg/day). The LOEL was 4 ppm. The NOEL for brain (cerebrum) cholinesterase inhibition was 2 ppm in males and 4 ppm in females. The LOEL for brain (cerebrum) cholinesterase inhibition was 4 ppm in males and 24 ppm in females. The NOEL for liver acetylcholinesterase and butyryl cholinesterase inhibition was 4 ppm in males and 2 ppm in females. The LOEL was 24 ppm in males and 4 ppm in females.

The NOEL for systemic toxicity was 24 ppm (males: 0.692 mg/kg/day; females: 0.702 mg/kg/day). The LOEL was > 24 ppm.

<u>Dose and Endpoint for Risk Assessment</u>: NOEL of 0.08 mg/kg/day, based on RBC cholinesterase inhibition at 0.17 mg/kg/day at 4 weeks.

<u>Comments on Study/Endpoint</u>: This NOEL of 0.08 mg/kg/day is supported by the NOEL of 0.05 mg/kg/day established for brain cholinesterase inhibition at four weeks in the mouse 4-week study [MRID 00117996]. Although there is a 21-day dermal toxicity study available on Propetamphos in rabbits, it was determined that it was not appropriate for use in this risk assessment because (1) the dog and mouse appear more sensitive than the rabbit; (2) no cholinesterase inhibition measurements were performed in the acute neurotoxicity study; and (3) comparable cholinesterase inhibition measurements were not obtained in the rabbit following oral dosing for comparison to the dermal study. Since an oral NOEL was identified, a dermal absorption factor of 100% should be used for this risk assessment.

This risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

<u>Study Selected</u>: see under Short-Term Risk Assessment.

This risk assessment is required.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: see under Short-Term Risk Assessment.

This risk assessment is required.

5. Inhalation Exposure (Any Time Period)

Study Selected: 14-Day Inhalation - rat [50% a.i.] §82-4

MRID No.00085156

Executive Summary: In a subchronic inhalation study, Sprague-Dawley/SIV rats (10/sex/group) were exposed (whole body) to safrotin (50% a.i.) for 14 days at concentrations of 0, 0.053, 0.097, 0.304, or 1.009 mg/L. Actual exposures occurred only on the 1st to 5th and 8th to 12th test days. Toxicity was monitored by clinical observations(daily), body weights (weekly), food consumption (daily), hematology (survivors), clinical chemistry (survivors), urinalysis (pretest and on days 3, 7, 10 and 14 in survivors), and at study termination, ophthalmology, auditory function, organ weights, necropsy observations and microscopic evaluation. Blood plasma and red blood cell cholinesterase activities were measured pretest and on days 3, 7, 10 and 14 in survivors.

At 1.009 mg/L, 11 deaths occurred during the first week of exposure (exposures were discontinued for this group after 7 days), and at 0.304 mg/L, 12 animals died by the end of the second week. No deaths occurred at 0.097 or 0.053 mg/L.

Clinical signs of toxicity at 0.097-1.009 mg/L included exophthalmos, ataxia, piloerection, and apathy. Additionally, at 0.304-1.009 mg/L, the rats became periodically cataleptic. No signs of toxicity were observed at 0.053 mg/L.

Mean body weights were decreased significantly compared to controls in female rats exposed to 0.097 mg/L (7%, not toxicologically significant) and both sexes at 0.304 mg/L (28-29%) after 14 days, and in both sexes at 1.009 mg/L after 5 days. Food consumption was also decreased at 1.009 mg/L. At all other exposure levels, food consumption was similar to controls.

Changes in hematology and clinical chemistry parameters were observed at the three highest exposure levels. At 0.097 mg/L, there was a dose-related decrease in leucocytes (12-40%). At 0.304 mg/L, decreases in hematocrit (9-16%), erythrocytes (15-19%), hemoglobin (18-21%), and lymphocytes (16-23%), and increases in neutrophils (85-90%) were observed. The differences for erythrocytes and hemoglobin were significant at 0.304 mg/L in both sexes and for hematocrit in males. For the 1.009 mg/L group, data obtained during the first 5 days of exposure were not analyzed statistically because of high mortality. In females, serum cholinesterase activities were statistically significantly decreased (43-79%) at all time periods at which measurements were made (days 3, 7 and 10) throughout the exposure period. In males, statistically significant inhibition (19-62%) of serum cholinesterase activities were observed at all measurement times for the 0.097 mg/kg/day group, but only at days 3 (54%) and 10 (65%) for the 0.304 mg/kg/day group, and only at day 10 (43%) for the 0.053 mg/kg/day group. There were no statistically significant changes in erythrocyte cholinesterase levels. Serum glucose was significantly reduced at 0.097 (24-25%) and 0.304 (31-42%) mg/L. Significant increases were noted at these exposure levels for SGPT (29-52%), SGOT (22-45%) and, except females at 0.097 mg/L, alkaline phosphatase (15-44%) .

Stomach hemorrhage observed at necropsy in the 0.097-1.009 mg/L exposure groups correlated with the microscopic observations of hemorrhagic erosions. Most of the rats that died during the study were reported to have pulmonary changes, and these correlated with the microscopic observations of lung congestion, edema, and emphysema, as well as inflammation of the trachea. There was no gross or microscopic pathology at 0.053 mg/L.

The systemic LOEL was 0.097 mg/L (corresponding to 0.049 mg/L a.i.) based on an increased incidence of clinical signs of toxicity, decrease in leukocyte counts, alterations in clinical chemistry parameters and gross and microscopic necropsy changes. The systemic NOEL was 0.053 mg/L (corresponding to 0.027 mg/L a.i.). The LOEL for serum cholinesterase inhibition was 0.053 mg/L (23% decrease [not stat. sig.] in males; 43% decrease [$p \leq 0.01$] in females at 3 days - earliest measurement); a NOEL was not established. The LOEL for erythrocyte cholinesterase inhibition was > 0.304 mg/L (corresponding to 0.152 mg/L a.i.). The NOEL was   0.304 mg/L. (ChE levels were not measured after Day 3 for the 1.009 mg/L group.)

<u>Dose and Endpoint for Risk Assessment</u>: LOEL = 0.027 mg/L (0.053 mg/L of 50% formulation), based on inhibition of plasma cholinesterase activity in males and females at 3 days (NOEL not determined).

<u>Comments about Study/Endpoint</u>: Although this 14-day inhalation toxicity study was conducted using a 50% a.i. formulation of propetamphos, the only inhalation data available on technical propetamphos is the acute inhalation toxicity data (MRID 41529301). The LC50 is 1.5 mg/L (males)/0.69 mg/L (females), which is a Toxicity Category III. Due to the lack of a NOEL, an additional Uncertainty Factor (UF) of 3 is required for this assessment.

This risk assessment is required.

D. Recommendation for Aggregate Exposure Risk Assessments

For short-term and intermediate-term risk assessments, calculate separate MOE's for dermal and inhalation exposures. For short-term and intermediate-term dermal exposure, an MOE of 100 is acceptable. For short-term and intermediate-term inhalation exposure, an MOE of 300 is acceptable. Therefore, for aggregate risk, the ARI method should be used. The MOE's can be combined for the dermal and inhalation routes, due to the common toxicity endpoint [cholinesterase inhibition].

For chronic risk assessment, convert the dermal and inhalation exposures [using 100% absorption for both routes] to oral equivalents and compare to the chronic RfD.

For cancer risk assessment, combine the dermal and inhalation exposures, using 100% absorption for both routes and compare to Q*1 or the NOEL [point of departure], as appropriate.

III. CLASSIFICATION OF CARCINOGENIC POTENTAIL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 00164890 and 42399001

Discussion of Tumor Data Females displayed a slight increase in the incidence of islet cell adenomas of the pancreas, which exceeded that of the historical control. The data have been submitted to SAB for analysis.

Adequacy of the Dose Levels Tested Based on the magnitude of the cholinesterase inhibition [plasma, RBC, and brain], the doses are considered adequate.

2. Carcinogenicity Study in Mice

MRID Nos. 00063021 and 00102928

Discussion of Tumor Data There were no treatment-related increases in the incidences of tumors observed in propetamphos-treated animals as compared with control animals.

Adequacy of the Dose Levels Tested Dose levels were adequate as evidenced by a dose-related inhibition of cholinesterase activities in plasma (87-89%), red blood cells (87-91%), brain (74-79%), and liver (50-69%) in both sexes. In addition, high-dose (21.0 mg/kg/day) females displayed a greater mortality rate (60%) than controls (45%) and a shorter median survival time (623 days vs. 645 days, respectively). Food consumption was significantly reduced in both sexes at the high dose (21.0 mg/kg/day), but no significant effects on body weight or body weight gain were observed in either sex.

3. Mutagenicity Data

MRID Nos. 41607405, 41607406, 41607403

Propetamphos was negative in both *in vivo* and *in vitro* studies at adequate dose levels.

Propetamphos is scheduled for review by the HED Cancer Assessment Review Committee.

IV. FQPA CONSIDERATIONS

1. Neurotoxicity: Propetamphos was not a delayed neurotoxicant in the hen. Neurotoxic effects were observed in the rat following an acute oral exposure. The NOEL for acute neurotoxic effects in rats is 6 mg/kg, based on alterations in the FOB and motor activity parameters at two hours post dose at 40 mg/kg, which included for both sexes, tremors, muscle fasciculations, flattened posture, decreased number of rears, impaired gait, decreased fore- and hind-limb grip strength, absence of pupil response, decreased rectal temperature [females only], abnormal righting reflex, and decreased motor activity. It is to be noted that cholinesterase activity was not monitored in this acute study in rats. In the 90-day subchronic neurotoxicity study, the NOEL for FOB and motor activity is 27 ppm [2.7 mg/kg/day] and the LOEL is 120 ppm [12 mg/kg/day], based on an increased incidence of uncoordinated righting reflex in males and slow pupillary response in females. The NOEL for cholinesterase activity inhibition is 6 ppm [0.6 mg/kg/day], based on significant inhibition of plasma and RBC cholinesterase activities at 27 ppm and 120 ppm. Significant inhibition of brain cholinesterase activity was observed at 120 ppm in both sexes. A substantial recovery of plasma, RBC, and brain cholinesterase activity occurred 3 weeks after termination of treatment in the high-dose males and females. There were no treatment-related neuropathological findings in either sex.

EVIDENCE OF NEUROTOXICITY FROM OTHER ORAL TOXICITY STUDIES

In the 2-year rat chronic toxicity study, there was a dose-related decrease in plasma and RBC cholinesterase activity in both sexes [NOEL of 6 ppm, LDT], and the high-dose group [120 ppm] displayed a moderate [34-40%] inhibition in brain cholinesterase. There were no clinical signs of toxicity.

In the mouse carcinogenicity study in both sexes at dose levels of 1 mg/kg/day and above, there was an inhibition of erythrocyte [males 20%-87%; females 33%-91%], plasma [males 23%-89%; females 20%-87%], brain [males 51%-74%; females 58%-79%], and liver [males 44%-69%; females 25%-50%] cholinesterase activities throughout the study. High-dose [21 mg/kg/day] males displayed an increase in brain vacuolation and high-dose females displayed an increase in neural vacuolation. There were no clinical signs of toxicity.

Decreases in plasma, RBC, and brain cholinesterase activity were observed in a 4-week/ 8-week feeding study in mice in which no clinical signs of cholinesterase inhibition were noted.

In the chronic toxicity study in dogs, tremors were observed at dose levels of 100 ppm and above and cholinesterase inhibition was observed at dose levels of 20 ppm and above.

During the pre-mating period, F0 and F1 females at the high-dose level [75 ppm] displayed hyperreflexia and tremors in the 2-generation reproduction study in rats. Additionally, there were significant decreases in cholinesterase activities [acetyl-, butyryl- RBC, and brain] in the mid- [30 ppm] and high-dose levels in both generations.

In a range-finding developmental toxicity study in rabbits, all rabbits at the 40 mg/kg/day dose level died after the second day of dosing; before death, signs of ataxia, tremors, dyspnea, marked salivation, constricted pupils were observed. There were no clinical signs at the high-dose level [8 mg/kg/day] in the definitive rabbit study. In a pilot developmental toxicity study in rats, weakness, muscle twitching, and labored breathing were observed before death at 10 mg/kg/day. In the definitive rat study, drowsiness and muscle tremors were observed at the mid- and high-dose levels [3 and 6 mg/kg/day].

In 21-day dermal studies, cholinesterase inhibition and death were observed.

2. <u>Developmental Toxicity</u>: In a developmental toxicity study [Accession No. 254426, MRID 00142110], groups of Han Wistar rats containing 25/dose were administered Propetamphos in 2% gelatin (approx. 89% a.i.) by gavage at doses of 0, 1.5, 3.0 or 6.0 mg/kg/day from day 6 to 15 of gestation. Clinical signs of toxicity, including drowsiness, exophthalmus and muscle tremors, were observed in 24/25 animals in the 6.0 mg/kg/day group and 15/23 animals in the 3.0 mg/kg/day group. Animals in the 6.0 mg/kg/day group had decreased body weight gain (≈10%) in comparison to controls during the course of treatment. Weight gain in this group was increased after treatment was discontinued. There was no treatment-related effect on food consumption. There were no effects on maternal fertility or gestation indices, numbers of fetuses or litters, early and late resorptions, fetal sex ratio, number of live fetuses or fetal weight. All dams had live fetuses at necropsy and there were comparable numbers of corpora lutea and implantations. Pre- and post-implantation loss was comparable among control and treated groups. There were no abortions, premature deliveries, dams with 100% uterine deaths or dead fetuses. There was no evidence of a developmental effect at any treatment level, based on visceral, external and skeletal examinations of the fetuses.

Maternal LOEL = 3.0 mg/kg/day based on clinical signs of toxicity; maternal NOEL = 1.5 mg/kg/day; Developmental LOEL = >6.0 mg/kg/day; developmental NOEL = 6.0 mg/kg/day, highest dose tested.

In a developmental toxicity study (MRID 92150015), Propetamphos technical (92% a.i.) was administered to pregnant female New Zealand White rabbits (15/dose, except for 14 at the high dose) by gavage (as a suspension in 0.5% carboxymethyl cellulose) at dose levels of 0 (0.5 mL vehicle only), 1.0, 4.0, or 8.0 mg/kg body weight/day from days 6 through 18 of gestation.

Propetamphos technical exerted no effects on maternal mortality, clinical signs, or the incidence of findings at gross necropsy. At the high-dose (8 mg/kg/day) level, there was a statistically significant decrease in body weight change during the treatment period (-45 g for high-dose females; +119 g for controls). At sacrifice, corrected body weight (weight at sacrifice minus gravid uterus weight) was slightly, but significantly decreased (92% control value) for the high-dose (8 mg/kg/ day) group. **The maternal LOEL is 8.0 mg/kg/day (HDT), based on decreased body weight change during the treatment period and decreased corrected body weight at sacrifice. The maternal NOEL is 4.0 mg/kg/day.**

The only treatment-related developmental effects observed were the increased absolute number of resorptions (15 in high-dose group; 7 in controls; not statistically significant) observed in the high-dose (8 mg/kg/day) group, and the resulting increases in the resorptions/doe and post-implantation loss for this group. No treatment-related malformations or variations were observed. **The developmental LOEL is 8.0 mg/kg/day (HDT), based on an increased absolute number of resorptions and resulting increases in resorptions/doe and post-implantation loss. The developmental NOEL is 4.0 mg/kg/day.**

<u>Reproductive Toxicity</u>: In the 2-generation reproduction study [MRID 43039801] in Wistar Crl:(WI)br-derived [SPF] rats [25/sex/dose], Propetamphos [91.8%] was administered at dietary levels of 0, 4, 30, and 75 ppm [♂♂ 0.3, 2.1, and 5.5/♀♀ 0.4, 2.8, and 7.1 mg/kg/day, respectively] for 70 days [F_0 parental rats] prior to mating [1 ♂:1 ♀]; F_1 pups were selected for next generation at 21 days of age and were ≈16 weeks old [≈105 days] at mating. There was one litter per generation.

Systemic toxicity, as evidenced by hyperreflexia and tremors, was observed in the F_0 and F_1 females at the high-dose level [mainly during premating period]. Decreased body-weight gain was observed during weeks 0-5 of the premating period in F_0 females [82% of control] and during both the F_0 [87.5% of control] and F_1 [83.4% of control] gestation periods at the high-dose level. Body-weight gain was also decreased at the mid-dose level in F_0 females during weeks 0-5 of the pre-mating period and in the F_1 females during gestation. At the high-dose level of the F_1 females, there were significant decreases in the mating index [96% for controls <u>vs</u> 70% for the high dose], the lactation index [85% for controls <u>vs</u> 40% for the high dose], and the viability index [93% for controls <u>vs</u> 81% for the high dose]. Female fertility index was also decreased at the high-dose level of the F_1 females compared to the controls [91% <u>vs</u> 81%, respectively], but statistical significance was not attained. The lactation index for the F_0 dams was significantly decreased [99% for controls <u>vs</u> 81% for the high dose]. None of the other indices was adversely affected in the F_0 generation. There was no increase in the number of stillborn pups with dose, and the live birth index was comparable among the groups for both generations. Litter size was comparable among the F_1 litters, but there was a decrease in litter size at the low- [86.8% of control] and high-dose [80.6% of control] levels in the F_2 litters. Treatment-related pup mortality was evident in both generations. For the high-dose F_1 pups, there was a significant increase in the number dying during lactation days 5-7 and days 8-14 compared to the controls. For the high-dose F_2 pups, there was a significant increase in the number dying during lactation days 1-4, days 5-7, days 8-14, and days 15-21 compared to the controls. Also noted was a decrease in the number of implantation sites in the treated groups compared to the controls for both generations, but a significant decrease was observed only at the high-dose level [79% of control] of the F_1 generation.

At necropsy, there were significant decreases in cholinesterase levels in the mid- and high-dose parental rats of both generations. Brain cholinesterase was significantly decreased in the high-dose F_0 males [43.4%], and in the mid- and high-dose F_0 females [44.8% and 64.7%, respectively], F_1 males [19.7% and 46.1%, respectively], and F_1 females [47.5% and 60.7%, respectively], with the females displaying the larger decrease. Both acetylcholinesterase and butyrylcholinesterase were significantly decreased at both the mid- and high-dose levels in both sexes in both generations. For acetylcholinesterase, decreases in the mid- and high-dose groups ranged from 31% to 60% in males and 51% to 81% in females. For butyrylcholinesterase, decreases in the mid- and high-dose groups ranged from 36% to 74% in males and 51% to 80% in females. The decrease in RBC cholinesterase was minimal in the F_0 parental rats [4%-8%] and somewhat greater in the F_1 parental rats [10.4%-14.4%]. There was a dose-related increase in the number of runts at the mid- and high-dose level in the F_1 generation. In the F_2 generation, only treated pups were found partly cannibalized, with the number at the high-dose being statistically significant. It is not apparent whether this is due to defective pups or is a behavioral effect. In both generations, the number of pups autolyzed was significantly increased at the high-dose level, and a greater number of high-dose F_1 pups and F_2 pups at all dose levels had no milk in the stomach. At the high-dose level in both sexes, F_1 pups displayed decreased body weight on day 21 of lactation [85% of control], and body-weight gain [83% of control] was also decreased compared to the control. F_2 males displayed body weight and body-weight gains that were comparable to the control males, but the high-dose F_2 females displayed decreased body weight on day 21 of lactation [87% of control; not statistically significant] and decreased body-weight gain [85% of control]. The high-dose F_1 pups displayed significantly decreased levels of acetylcholinesterase [♂♂ 38.4%/♀♀ 39.2%], butyrylcholinesterase [♂♂ 43.6%/♀♀ 42%], RBC cholinesterase [♂♂ 8.8%/♀♀ 14.9%], and brain cholinesterase [♂♂ 17.6%/♀♀ 19.3%] in both sexes, and the mid-dose females displayed a statistically significant decrease in RBC cholinesterase [10.1%]. In the F_2 pups, statistically-significant decreases were observed in (1) acetylcholinesterase in the high-dose males [44.7%] and in the mid- [14.9%] and high-dose [41.3%] females; (2) butyryl-cholinesterase at the mid-dose level in females [16.3%] and at the high-dose level in both sexes [♂♂ 46.6%/♀♀ 41.1%]; and (3) RBC cholinesterase in males at the high-dose level [14.5%]. No treatment-related changes were reported in liver weights in either generation, and no histopathological changes were found in any of the organs examined [liver and sex organs] that could be attributed to treatment. The brain was not weighed.

The NOEL for cholinesterase inhibition [acetyl-, butyryl, RBC, and brain cholinesterase] in the parental rats is 4 ppm [♂♂ 0.3/♀♀ 0.4 mg/kg/day], and the LOEL is 30 ppm [♂♂ 2.1/♀♀ 2.8 mg/kg/day]. For F_1 and F_2 pups, the NOEL for cholinesterase inhibition [acetyl-, butyryl, RBC] is 4 ppm [♂♂ 0.3/♀♀ 0.4 mg/kg/day], and the LOEL is 30 ppm [♂♂ 2.1/♀♀ 2.8 mg/kg/day]. The NOEL for brain cholinesterase inhibition in the F_1 pups is 30 ppm [♂♂ 2.1/♀♀ 2.8 mg/kg/day], and the LOEL is 75 ppm [♂♂ 5.5/♀♀ 7.1 mg/kg/day]. The NOEL for brain cholinesterase in the F_2 pups is 75 ppm. The NOEL for parental systemic toxicity is 30 ppm [♂♂ 2.1/♀♀ 2.8 mg/kg/day], and the LOEL is 75 ppm [♂♂ 5.5/♀♀ 7.1], based on hyperreflexia and tremors in females and decreased body-weight gains during weeks 0-5 of premating and during the F_0 and F_1 gestation periods. The reproductive/developmental NOEL is 30 ppm, and the LOEL is 75 ppm, based on decreases in the mating index [F_1], lactation index [F_0 and F_1], and viability index [F_1], decreased number of implant sites [F_1], decreased litter size [F_0 (days 14 and 21)/F_1 (throughout) generations], increased number of runts [F_1 pups], increased pup mortality [both generations], and decreased pup body-weight gain [both

generations].

4. Determination of Susceptibility

There is no evidence of increased susceptibility, based on adequate developmental toxicity studies in rats and rabbits and an adequate 2-generation reproduction study in rats. There is evidence of neurotoxicity/cholinesterase inhibition in rats, rabbits, mice, and dogs. The NOEL for brain cholinesterase inhibition is 4 ppm in adults, 30 ppm in F1 pups and 75 ppm in F2 pups [rats]. The NOEL for cholinesterase inhibition [acetyl-, butyryl-, and RBC] is the same for the parental, F1, and F2 pups [4 ppm].

5. Recommendation for a Developmental Neurotoxicity Study

(i) Evidence that suggests requiring a developmental neurotoxicity study:

Propetamphos is an organophosphate [OP]. Plasma, RBC, and brain cholinesterase inhibition have been observed in all species [rat, mouse, dog, rabbit] following short- and long-term exposure and the oral, dermal, and inhalation routes of exposure. Clinical signs of neurotoxicity [tremors, drowsiness, muscle tremors, fasciculations, apathy] have been observed. Brain [male]/neural [female] vacuolation were observed in the mouse carcinogenicity study at the high-dose level.

(ii) Evidence that **do not** support a need for a developmental neurotoxicity study:

There is no evidence of delayed neuropathology in the hen, neuropathology has not been observed in the rat following acute and subchronic [perfused and non-perfused] and long-term exposures [non-perfused], and no brain weight effects have been observed.
There is no evidence of developmental anomalies in the fetal nervous system in the prenatal developmental toxicity studies in rats and rabbits.

The available evidence does not appear to provide adequate justification for a requirement of a developmental neurotoxicity study at this time.

V. DATA GAPS

There are no data gaps.

VI. HAZARD CHARACTERIZATION

Propetamphos is an aliphatic organophosphate [(E)-1-methylethyl-3-[[(ethylamino) methoxyphosphinothioyl]oxy]-2-butanoate registered for use as an insecticide effective against cockroaches, mosquitoes, and fleas.The toxicology data base provides evidence that Propetamphos has anticholinesterase activity, as evidenced by clinical signs [ataxia, tremors, salivation, constricted pupils, muscle tremors, dypsnea, weakness] in rats [subchronic/oral and inhalation], rabbits [gavage/short-term], and dogs [chronic] and decreased cholinesterase activity in rats, mice, and dogs following subchronic and chronic exposures and in rabbits following subchronic dermal exposure. In acute toxicity studies, Propetamphos exhibits low to high toxicity, depending on the route of exposure. Propetamphos is acutely toxic at low oral dose levels and *via* the oral and dermal routes in rats and rabbits, respectively. In rats, Propetamphos is not acutely toxic *via* the inhalation route, is non-irritating to the skin, is not a dermal sensitizer, and is not an eye irritant in the rabbit. Propetamphos did not cause acute delayed neurotoxicity in hens, and there was no evidence of neuropathology in the chronic study in rats [highest dose tested was 120 ppm (males 5.9/females 7.6 mg/kg/day)]. In the mouse chronic toxicity/carcinogenicity study, neural vacuolation was observed in females and brain vacuolation was observed in males at the high-dose level [21 mg/kg/day].

There is no indication of an increased sensitivity of offspring in rats or rabbits after prenatal and/or postnatal exposure to Propetamphos.There was no developmental toxicity observed in the rat at adequate dose levels that produced clinical signs in the dams [drowsiness, exophthalmus, and muscle tremors]. In rabbits, at the highest dose tested where no clinical signs were noted in the does and decreased body weight change/corrected body weight occurred, there was an increase in the absolute number of resorptions and resulting increases in resorptions/doe and post-implantation loss. In the 2-generation reproduction study in rats, hyperflexia and tremors were observed in the high-dose F0 and F1 females, mainly during the premating period. In the adult rats, plasma and RBC cholinesterase inhibition was observed at the mid- and high-dose levels in both sexes in both generations, and brain cholinesterase was decreased at the high-dose level in both the male and female F0 and F1 rats. The lactation index was decreased for the F0 dams, and significant decreases in the mating index, lactation index, fertility index, and viability index were observed for the high-dose F1 dams. Treatment-related pup mortality was evident in both generations at the high dose, and there was an increase in the number of F1 pups that were runts. Decreased plasma [mid- and high-dose F0 and F1 pups], RBC [mid- and high-dose F0 and F1 pups], and brain [high dose F0 pups] cholinesterase activities were observed in the offspring.

Propetamphos produced a slight increase in the incidence of islet cell adenomas in the pancreas of female Sprague-Dawley rats, but its classification has not been assessed by the HED Cancer Assessment Review Committee to date.

CHOLINESTERASE INHIBITION

MOUSE Cholinesterase inhibition [brain, RBC, plasma, and liver] was observed in mice [both sexes] at dose levels of 1 mg/kg/day and above in the carcinogenicity study in the absence of clinical signs dose levels up to 21 mg/kg/day. **RAT** In the chronic rat study [6, 12, and 120 ppm (♂♂ 0.376, 0.632, and 5.891/♀♀ 0.412, 0.689, and 7.602 mg/kg/day], plasma and RBC cholinesterase were significantly decreased in both sexes at the mid- and high-dose levels, and brain cholinesterase inhibition was observed at the high-dose level in both sexes. Clinical signs [hyperflexia] were observed only at the high dose. In females, there was an increased incidence of focal atrophy of exocrine cells of the pancreas and a slight increase in the incidence of islet cell hyperplasia and adenomas. There were significant decreases in cholinesterase activities [acetyl, butyryl, RBC, and brain] in the F0 and F1 female rats in the 2-generation reproduction study [4, 30, and 75 ppm (♂♂ 0.3, 2.1, and 5.5/♀♀ 0.4, 2.8, and 7.1 mg/kg/day)] at the mid- and high-dose levels, but clinical signs [hyperreflexia and tremors] were observed at the high-dose only. In the offspring, significant decreases in cholinesterase activities [acetyl, butyryl, and RBC] were observed in F1 and F2 pups at dose levels comparable to those of the adults; i.e., same NOEL and for brain cholinesterase inhibition at dose levels greater than in the adults [adult NOEL

4 ppm; F1 pup NOEL 30 ppm, F2 pup NOEL 75 ppm]. **DOG** Cholinesterase inhibition [plasma and RBC] was observed at lower dose levels in males than in females, and clinical signs [diarrhea and vomiting] occurred only at the high-dose [both sexes]. Brain cholinesterase inhibition was observed at the high dose only [males 21%/females 18%], where there was also evidence of regenerative anemia and hepatotoxicity [males].

Propetamphos is not a delayed neurotoxicant in the hen. In rats, neurotoxic effects [alterations in FOB (tremors, muscle fasciculations, flattened posture, decreased number of rears, impaired gait, decreased fore- and hind-limb grip strength, absence of pupil response, decreased rectal temperature, abnormal righting reflex) and decreased motor activity at 2 hours post dose] were observed following acute exposure, but no measurements of cholinesterase activity or NTE were performed. In the 90-day neurotoxicity study, there was an increase in the incidence of uncoordinated righting reflex in males and slow pupillary response in females at the highest dose tested. Brain cholinesterase inhibition was observed at the high dose in both sexes, and plasma and RBC cholinesterase inhibition was observed at the mid- and high-dose levels in both sexes. A substantial recovery of plasma, RBC, and brain cholinesterase activity occurred following 3 weeks without exposure to Propetamphos. No treatment-related neuropathological findings were observed in either sex.

VI SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOEL 0.05	Brain cholinesterase inhibition	Mouse 4-Week Oral Toxicity
Chronic Dietary non-carcinogenic effects	NOEL=0.05 (UF=100)	Decreased brain, RBC, and plasma cholinesterase	Mouse Chronic Toxicity/Carcinogenicity
		Chronic RfD = 0.0005 mg/kg/day	
Chronic Dietary carcinogenic effects		To be determined after Cancer Assessment Review Commiteee meeting	
Short-Term* (Dermal)	NOEL = 0.08	RBC cholinesterase inhibition	6-Month -Dog
Intermediate-Term* (Dermal)			
Chronic Dermal* non-carcinogenic effects			
Chronic Dermal* carcinogenic effects		To be determined after Cancer Assessment Review Commiteee meeting	
Inhalation (Any Time Period)	LOEL 0.027 mg/L	plasma cholinesterase inhibition.	

* Since an oral NOEL was selected a 100% dermal absorption factor should be used for this risk assessment

VIII. ACUTE **TOXICITY ENDPOINTS:**

Acute Toxicity of Propetamphos

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral - rat	41607417	LD_{50} = 116.1 mg/kg (80.3-198.0) Males = 96.4 mg/kg (576-151.9) Females = 105.7 mg/kg (85.9-133.4) Combined	II
81-2	Acute Dermal - rabbit	41607418	LD_{50} = 486.4 mg/kg (Combined; 369.4-653.9)	II
81-3	Acute Inhalation - rat	41529301	LC_{50} = 1.5 mg/L (1.15-1.89) Males = 0.69 mg/L (0.58-0.90) Females	III
81-4	Primary Eye Irritation	41607419	The primary eye irriation score of Propetamphos based on the 1, 24, 48, and 72 hour observations was reported to be 0.	IV
81-5	Primary Skin Irritation	41607420	Not a primary dermal irritant; no erythema or edema at any time period.	IV
81-6	Dermal Sensiti-zation	41607412	Not a dermal sensitizer.	N/A
81-7	Acute Delayed Neurotoxi-city (Hen)	00029976 92150004 92150013	Acute LD_{50} = 78 mg/kg (48-108 95% C.I.) Not a delayed neurotoxicant.	N/A
81-8	Acute Neurotoxicity - rat	43403901	NOEL = 6.0 mg/kg, based on various neurotoxic effects at Day 0 at 40 mg/kg (LOEL; ChE activities were not measured)	N/A